High rate of breakthrough invasive aspergillosis among patients receiving caspofungin for persistent fever and neutropenia

M. Lafaurie[1], J. Lapalu[2], E. Raffoux[3], B. Breton[4], C. Lacroix[5], G. Socié[6], R. Porcher[7], P. Ribaud[6], S. Touratier[2] and J.-M. Molina[8]

1) *Infectious Diseases Intervention Unit, Saint-Louis Hospital,* 2) *Pharmacy, Saint-Louis Hospital,* 3) *Hematology, Saint-Louis Hospital,* 4) *Pediatric Hematology Unit, Saint-Louis Hospital,* 5) *Parasitology and Mycology Laboratory, Saint-Louis Hospital,* 6) *Hematology-Bone Marrow Transplantation Unit, Saint-Louis Hospital,* 7) *Biostatistics Department, Saint-Louis Hospital and* 8) *Department of Infectious Diseases, Saint-Louis Hospital, Paris, France*

Abstract

A number of agents are now available for empirical antifungal treatment (EAFT) of patients with persistent fever and neutropenia. We carried out a study of efficacy of antifungal drugs to prevent breakthrough invasive aspergillosis by reviewing the medical records of all consecutive patients who received EAFT from November 2005 to February 2006. Patients' characteristics and the type, dose and duration of antifungal therapy were recorded. Breakthrough invasive fungal infections were documented according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definition. Fifty-six episodes of persistent fever with neutropenia requiring EAFT were recorded among 49 patients. All patients received high-dose chemotherapy for acute myeloid leukaemia (51%), acute lymphoid leukaemia (12%), lymphoma (14%) or other haematologic conditions (22%). Fourteen (29%) and five (10%) patients were allogeneic and autologous haematopoietic stem cell transplant recipients, respectively. Caspofungin was prescribed initially in 40 episodes (71%), amphotericin B (AmB) desoxycholate and liposomal AmB being prescribed in six (10%) and ten (18%) episodes, respectively. Six patients were switched from liposomal AmB to caspofungin because of adverse events. The median duration of antifungal therapy was 9 days. During follow-up, six patients (12%) were diagnosed with invasive aspergillosis after a median of 8 days (range 3–16 days) of EAFT. Invasive aspergillosis breakthrough occurred in 6/46 (13%) caspofungin recipients and in 0/16 (0%) AmB recipients (OR 3.1, p 0.32). The observed high rate of invasive aspergillosis among caspofungin recipients requires further evaluation.

Keywords: Aspergillosis, breakthrough, caspofungin, empirical, neutropenia
Original Submission: 8 May 2009; **Revised Submission:** 25 August 2009; **Accepted:** 27 August 2009
Editor: M. Cavling-Arendrup
Article published online: 3 September 2009
Clin Microbiol Infect 2010; **16**: 1191–1196
10.1111/j.1469-0691.2009.03050.x

Corresponding author and reprint requests: M. Lafaurie, Infectious Diseases Intervention Unit, Hôpital Saint-Louis, 1 avenue Claude Vellefaux, 75010, Paris, France
E-mail: matthieu.lafaurie@sls.aphp.fr

Introduction

The role of invasive fungal infections (IFI) as the leading cause of death in cancer patients with prolonged neutropenia [1,2] and clinical observations showing the importance of early treatment in the prognosis of IFI [3] have led to the concept of empirical antifungal therapy as a treatment strategy in patients with persistent fever and neutropenia. Two small randomized trials, which did not comply with modern methodological requirements, laid the scientific foundation for the use of amphotericin B (AmB) desoxycholate as empirical antifungal therapy (EAFT) in these patients [4,5]. More recently, liposomal AmB and caspofungin, but not voriconazole, have been approved for EAFT [6–8]. The recent availability of less toxic antifungal agents may have facilitated the uninformed and inappropriate prescription of these drugs, with the potential risks of insufficient efficacy and selection of resistant fungal strains. Over the last few years in our institution, there has been an increased prescription of caspofungin, and a parallel decrease in prescription of AmB. To better understand the way in which physicians prescribe antifungal agents in patients with febrile neutropenia, and to assess the efficacy and safety of this strategy, we undertook a prospective 3-month audit of EAFT in our institution.

Materials and Methods

The Saint-Louis hospital is a 650-bed tertiary hospital with major clinical activities in haematology and oncology. The present study was carried out by reviewing the medical records of all consecutive patients admitted to the haematology, oncology, intensive care unit and infectious diseases wards and treated with EAFT between 7 November 2005 and 7 February 2006.

EAFT was defined as the use of antifungal agents in patients with neutropenia and persistent or recurrent fever despite broad spectrum antibiotics, and without clinical or radiological signs of IFI. Neutropenia was defined by an absolute neutrophil count $<500/mm^3$ or $<1000/mm^3$ but was expected to drop $<500/mm^3$ within 48 h. Patients with total leucocyte count $<1000/mm^3$ after chemotherapy and without a neutrophil count available, were also considered to fulfill the definition of neutropenia.

Fever was defined as a temperature ≥38°C over 1 h or ≥38.3°C once. Voriconazole, caspofungin and liposomal AmB were delivered by the central pharmacy of our institution using restrictive nominative formularies but AmB desoxycholate was not.

Pharmacists were asked to identify all orders for EAFT from their records. Nurses were asked about any new prescription of unrestricted AmB desoxycholate each week. One infectious diseases specialist and one pharmacist, both members of the Infectious Diseases Intervention Unit, collected information from each treated patient chart and analyzed the data once the antifungal drug had been stopped aiming to avoid interfering with the prescription. The data recorded were: demographic characteristics, date and ward of admission, underlying disease, type of chemotherapy and antimicrobial therapy, presence of fever, leucocyte and absolute neutrophil count, serum creatinine level, concomitant use of nephrotoxic agents at the initiation of the EAFT, current or prior (co)administration of antifungal drugs (3 months before EAFT initiation), resolution of fever under antifungal treatment, breakthrough IFI and mortality. A breakthrough IFI wad defined as any IFI diagnosed after ≥3 days of EAFT, as proposed in a study by Walsh *et al.* [7] comparing caspofungin and liposomal AmB in patients with persistent fever and neutropenia. Galactomann blood index (threshold 0.5, enzyme-linked immunosorbent assay, Ag Aspergillus; Bio-Rad. Hercules, CA, USA) was measured once a week in the bone marrow transplantation unit and chest computed tomography (CT) was performed before the transplantation. No routine diagnostic procedure was performed in other units unless an IFI was suspected.

If information was missing in the medical, laboratory and/or nurse charts, the medical team was interviewed to collect the missing data. Pharmacology parameters were also recorded regarding the doses, intervals between administration and length of treatment for each antifungal agent. If a patient was treated for two or more distinct episodes of fever and neutropenia during the 3-month study period, each episode was analyzed independently.

Results

Overall, 56 EAFT episodes among 49 patients were retained for analysis (seven patients had two separate febrile neutropenia episodes).

Forty-four patients were male (90%) and the median age was 41 years (range 15–76 years). Forty-five patients (92%) were hospitalized in the haematology or oncology unit, four in the intensive care unit. Thirty-one patients (63%) were treated for acute leukaemia (25 acute myeloid leukaemia and six acute lymphoid leukaemia), seven (14%) for lymphoma and 11 (22%) for other haematologic conditions. Fourteen patients (29%) were allogeneic haematopoietic stem cell transplant (HSCT) recipients and five (10%) had undergone an autologous stem cell transplant. Antifungal prophylaxis (oral fluconazole in all cases) was prescribed in 23 patients (47%) after the administration of chemotherapy and before the beginning of the EAFT.

EAFT was started because of persistent fever despite broad-spectrum antibiotics (22 episodes, median duration of fever 7 days), recurrence of fever after transient apyrexia under antibiotics (27 episodes), clinical signs of sepsis with temperature <38°C (three episodes) and tachycardia and elevated C reactive protein (two episodes).

A profound neutropenia (as defined as an absolute neutrophil count $<100/mm^3$) was noted in 23 episodes (41%). The median duration of chemotherapy-induced neutropenia was 28 days (range 1–61 days). EAFT was started after a median duration of neutropenia of 13 days (range 1–58 days).

First-line EAFT was caspofungin in 40 episodes (71%), AmB desoxycholate in six cases (11%) and liposomal AmB in ten cases (18%) (Fig. 1). In six episodes, liposomal AmB was switched to caspofungin for drug-related adverse events (renal insufficiency in four, infusion related chills in two). The median duration of EAFT was 9 days. Reasons for discontinuing EAFT were full neutrophil count recovery in 43 (77%) episodes, a suspected IFI as a result of *Aspergillus* in eight episodes (14%) (of which two were later not confirmed), patients discharged from hospital in two episodes (9%), and death in three episodes (5%). The doses and fre-

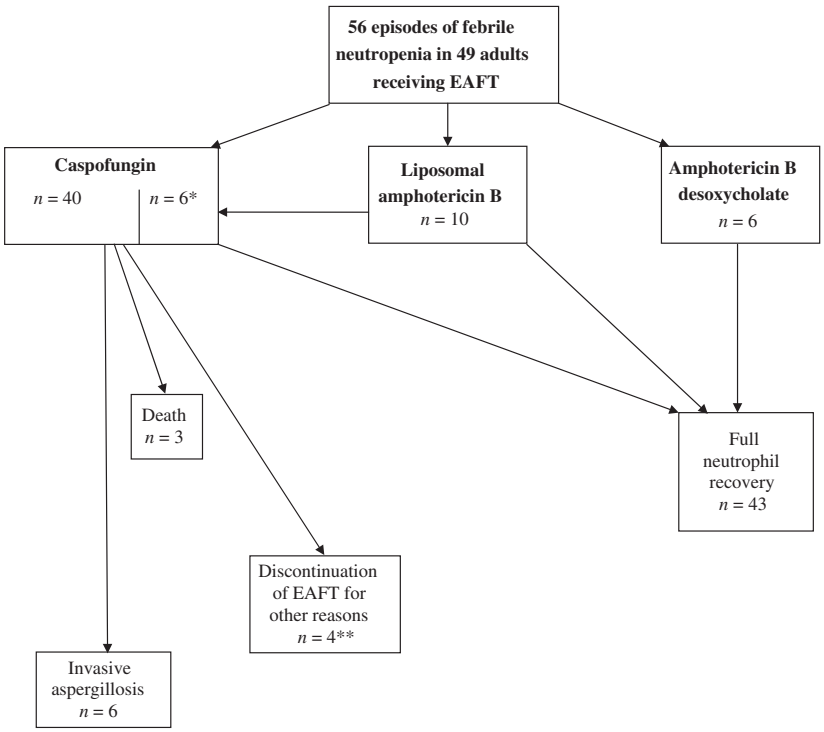

FIG. 1 Empirical antifungal therapies (EAFT) and outcome during 56 episodes of febrile neutropenia after chemotherapy among 49 patients. *Switch from liposomal amphotericin B (AmB) to caspofungin (n = 6) because of toxicity (renal insufficiency, n = 4) or side effects (infusion related chills, n = 2). **Suspected invasive aspergillosis (n = 2), hospital discharge (n = 2).

quencies of administration of antifungal agents were in agreement with current recommendations.

Eight suspicions of breakthrough invasive aspergillosis (IA) led to the interruption of the EAFT. In two patients, the diagnosis of IA was eventually not confirmed (false-positive *Aspergillus* galactomannan antigenemia as a result of tazocillin in one patient, contaminated blood culture with *Aspergillus* sp. in one patient). The diagnosis of IA was retained in six treated patients during the course of the EAFT (11% of episodes), after a median of 8 days (range 3–16 days) after EAFT initiation (Table 1). The site of infection was the lungs in all cases. Two patients had received prophylactic treatment with oral fluconazole (400 mg od) before EAFT. All patients had new infiltrates on chest X-ray. According to the 2008-revised European Organization for Research and Treatment of Cancer (EORTC) classification, there were three patients with possible IA and three with probable IA [9]. All patients then received voriconazole (together with caspofungin in one case). At the time that breakthrough IA was diagnosed, all patients were on caspofungin EAFT. IA emerged during six out of 46 episodes with caspofungin EAFT (13%) compared to none out of 16 episodes with AmB EAFT (desoxycholate and liposomal) (OR 3.1; median unbiased exact estimate, with 95% CI 0.42 to infinity, p 0.32 by Fisher's exact test).

No invasive fungal infection due to *Candida* or other fungi was reported throughout the study. Outcome review at the last study point (median 18 weeks after the study period) revealed that 14 patients died (28%) but only one death was related to IA.

Discussion

Fungal infections were recognized some decades ago as potential causes of persistent or recurrent fever in patients receiving antibiotics during an episode of neutropenia [1,4,5]. Various studies have demonstrated that patients with acute leukaemia and allogeneic HSCT recipients are at high risk of IFI as a result of prolonged and profound neutropenia and/or immunosuppression for graft-versus-host disease [10,11]. Most patients in the present study belonged to one or both of these conditions (acute leukaemia 63%, haematopoietic cell transplantation 29%) and were therefore at high risk of developing an IFI during episodes of febrile neutropenia. In addition, the median duration of chemotherapy-induced neutropenia among our patients was long (28 days, range 1–61 days) and neutropenia was severe, with an absolute neutrophil count <100/mm^3 in 41% of episodes; EAFT was started after a median duration of neutropenia of 13 days. The present study thus involved a much higher risk group of patients than those included in most other EAFT studies, which could explain the high incidence of breakthrough IA reported here.

The results obtained in the present study show that caspofungin was the preferred first-line EAFT at our institu-

TABLE 1. Invasive aspergillosis (IA) in patients treated with empirical antifungal therapy (EAFT) during febrile neutropenia

Age (years)	Underlying disease	Duration of neutropenia before IA diagnosis (days)	EAFT: drug(s) and duration before IA diagnosis	Classification of IA	Criteria for diagnosis	Chest CT scan signs	Microbiology
61	ALL	23	Caspofungin, 3 days	Probable	CT scan, GI-BAL+	Upper right lobar nodule, size 25 mm, surrounded by ground-glass attenuation	GI-BAL: 6.83 GI-B/week: all negative BAL, tracheal aspiration and sputum negative for *Aspergillus* or other pathogens
60	AML	62	Caspofungin, 9 days	Possible	Clinical signs, CT scan	Bilateral disseminated nodules, size 10 mm, surrounded by ground-glass attenuation	GI-B/week: all negative
43	Fanconi anemia, Allogeneic HSCT	94	Liposomal amphotericin B, 3 days then caspofungin, 16 days	Probable	Clinical signs, CT scan, GI-B+	Bilateral micro nodules and areas of ground-glass infiltrates	GI-BAL: 5 GI-B: 1.22 increasing to 4.01 BAL, tracheal aspiration and sputum negative for *Aspergillus* or other pathogens
48	AML	25	Amphotericin B 10 days, then caspofungin, 9 days	Possible	Clinical signs, CT scan	Bilateral disseminated nodules, size up to 25 mm and areas ground-glass infiltrates	GI-B/week: all negative GI-BAL: negative BAL, tracheal aspiration negative for *Aspergillus* or other pathogens
21	Severe aplastic anemia Allogeneic HSCT	28	Caspofungin, 7 days	Probable	Clinical signs, CT scan, GI-B+, GI-BAL+, culture	Nodules with halo sign	GI-BAL: 6.83 GI-B/week: all negative Sputum culture positive for *Aspergillus fumigatus* BAL, tracheal aspiration negative for *Aspergillus* or other pathogens
58	AML	19	Caspofungin, 3 days	Possible	CT scan signs	Bilateral disseminated nodules, size 25–40 mm, surrounded with ground-glass infiltrates	GI-B/week: all negative BAL, tracheal aspiration negative for *Aspergillus* or other pathogens

AML, acute myeloïd leukaemia; ALL, acute lymphoïd leukaemia; CT, computed tomography; HSCT, haematopoietic stem cell transplant; GI, galactomannan index; GI-B, GI in blood; GI-B+, two consecutive GI-B? 0.5 in blood; BAL, bronchoalveolar lavage; GI-BAL, GI in BAL; GI-BAL+, GI-BAL? 0.5.

tion because, overall, it was used in 41% of febrile neutropenic episodes, which is a much higher rate than in other European centers [12].

This wide use of caspofungin is likely a result of its favourable safety profile, especially its renal safety [7]. Indeed, in the present study, liposomal AmB was switched to caspofungin in six out of ten episodes because of renal toxicity. The high rate of renal toxicity with liposomal AmB compared to the studies conducted by Walsh *et al.* [7,8,13] was probably related to the use of this drug with other nephrotoxic agents in HSCT recipients.

No invasive *Candida* infection was found in the present study, which differs from the results of other large trials that have reported breakthrough invasive infections as a result of *Candida* in 0.5–3.5% of patients [7,8,13]. This discrepancy can be explained, in part, by the small size of the present study and the use of prophylactic fluconazole in 47% of our patients before EAFT.

The second important observation made in the present study is the very high rate of breakthrough IA (11%) among patients receiving EAFT. Although IA cases were only probable or possible according to the EORTC/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) definition, this rate of IA is much higher than that reported in recent comparative trials among patients receiving EAFT (<1–3% of patients) [7,8,13–16]. One possible explanation for this difference is the high-risk patient population involved in the present study. Indeed, subgroup analysis of patients at high risk in randomized trials have yielded IFI rates of up to 9.2% with liposomal AmB but only 1.4% with voriconazole [8]. A subgroup analysis of patients with acute myeloid leukaemia treated empirically with liposomal AmB or caspofungin, also yielded a breakthrough IFI rate of 7% in the caspofungin group and 5% in the liposomal AmB group [7]. These data also suggest that not all antifungal agents may have the same efficacy in preventing breakthrough IFIs, with better results being obtained with voriconazole and potentially worse results with caspofungin. Caspofungin is only fungistatic against *Aspergillus in vitro*, whereas voriconazole and liposomal AmB are fungicidal, and this might translate into lower clinical efficacy [17].

We were surprised to see all breakthrough IA cases occurring when patients were receiving EAFT with caspofun-

gin. Six cases were reported among 46 episodes treated with caspofungin compared to none among 16 patients treated with AmB. Although this difference was not significant, there was a trend towards a lower efficacy of caspofungin in preventing breakthrough IA in the present study. Several limitations might have contributed to this observation. First, the study was underpowered to show significant differences because of its small sampling size and short duration. Second, in the present study, we cannot exclude the possibility that patients being treated empirically with caspofungin were at higher risk of developing an IFI. Third, it is possible that some of IA was present at the start of EAFT but overlooked. Indeed, baseline invasive fungal infections have been reported in up to 5% of patients by Walsh *et al.* [7] and our patients did not undergo a chest CT scan at the start of EAFT. However, neither clinical, nor chest X-ray signs were noted in the patients charts before the diagnosis of IA, and surveillance with galactomannan assay is standard practice in our centre. Also, in the present study, we only considered IA diagnosed ≥3 days after starting EAFT, as suggested by Walsh *et al.* [7]. Interestingly, a recent study mentioned the occurrence of IA in nine high-risk patients (HSCT recipients) treated empirically with caspofungin, with *Aspergillus* isolates exhibiting high MIC to caspofungin in two cases [18]. Because caspofungin will be widely used as EAFT, these observations require further evaluation.

Nevertheless, caspofungin has been successfully used as salvage therapy for IA [19] and encouraging results have been reported in patients receiving chemotherapy or undergoing solid organ transplantation [20]. The experience with caspofungin as first-line therapy for IA has also been reported in two prospective trials with favourable response rates of 33% among patients with acute leukaemia and allogeneic HSCT recipients [21,22].

In conclusion, despite its limitations. the present study found a high rate of breakthrough IA among high-risk patients receiving caspofungin as EAFT, which is now widely used because of its favourable safety profile. Additional studies are required to confirm these results.

Acknowledgements

We are indebted to all the nurses who helped us with obtaining data from the patients and in antifungal treatments.

Transparency Declaration

All authors declare that there are no conflicting interests.

References

1. Bodey GP. Fungal infection and fever of unknown origin in neutropenic patients. *Am J Med* 1986; 80: 112–119.
2. Fraser IS, Denning DW. Empiric amphotericin B therapy: the need for a reappraisal. *Blood Rev* 1993; 7: 208–214.
3. Aisner J, Wiernik PH, Schimpf SC. Treatment of invasive aspergillosis: relation of early diagnosis and treatment to response. *Ann Intern Med* 1977; 86: 539–543.
4. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med* 1982; 72: 101–111.
5. EORTC International Antimicrobial Therapy Cooperative Group. Empiric antifungal therapy in febrile granulocytopenic patients. *Am J Med* 1989; 86: 668–672.
6. Cagnoni PJ, Walsh TJ, Prendergast MM *et al.* Pharmacoeconomic analysis of liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile neutropenic patients. *J Clin Oncol* 2000; 18: 2476–2483.
7. Walsh TJ, Teppler H, Donowitz GR *et al.* Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004; 351: 1391–1402.
8. Walsh TJ, Pappas P, Winston DJ *et al.* National Institute of Allergy and Infectious Diseases Mycoses Study Group. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; 346: 225–234.
9. De Pauw B, Walsh T, Donnelly J *et al.* Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; 46: 1813–1821.
10. De Gregorio MW, Lee W, Linker CA *et al.* Fungal infections in patients with acute leukaemia. *Am J Med* 1982; 73: 543–548.
11. Wald A, Leisenring W, Van Burik JA *et al.* Epidemiology of aspergillosis infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis* 1997; 175: 1459–1466.
12. Marchetti O, Cordonnier C, Calandra T. Empirical antifungal therapy in neutropenic cancer patients with persistent fever. Guidelines from the first European Conference on Infections in Leukaemia (ECIL). *Eur J Cancer* 2007; 5: 32–42.
13. Walsh TJ, Finberg RW, Arndt C *et al.* Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999; 340: 764–771.
14. Wingard JR, White MH, Anaissie E *et al.* A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. *Clin Infect Dis* 2000; 31: 1155–1163.
15. Winston DJ, Hathorn JW, Schuster MG *et al.* A multicenter, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy of febrile neutropenic patients with cancer. *Am J Med* 2000; 108: 282–289.
16. Boogaerts M, Winston DJ, Bow EJ *et al.* Intravenous and oral itraconazole versus intravenous amphotericin B depxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy. *Ann Intern Med* 2001; 135: 412–422.
17. Bartizal K, Gill CJ, Abruzzo GK *et al.* In vitro preclinical evaluation studies with the echinocandin antifungal MK-0991 (L-743,872). *Antimicrob Agents Chemother* 1997; 41: 2326–2332.
18. Madureira A, Bergeron A, Lacroix C *et al.* Breathrough invasive aspergillosis in allogeneic haematopoietic stem cell transplant

recipients treated with caspofungin. *Int J Antimicrob Agents* 2007; 30(6): 551–554.

19. Maertens J, Raad I, Petrikkos G *et al.* Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis* 2004; 39: 1563–1571.
20. Betts R, Glasmacher A, Maertens J *et al.* Efficacy of caspofungin against invasive *Candida* or invasive *Aspergillus* infections in neutropenic patients. *Cancer* 2006; 106: 466–473.
21. Viscoli C, Herbrecht R, Akan H *et al. Caspofungin (C) as First-line therapy of invasive aspergillosis (IA) in haematological patients (pts): a study of the EORTC Infectious Diseases Group*. Abstract n° O.12, 3rd TIMM, Torino: 2007.
22. Herbrecht R, Maertens J, Baila L *et al. Caspofungin as first-line therapy of invasive aspergillosis in allogeneic hematopoietic stem cell transplant recipients: a study of the EORTC infectious diseases group*. Abstract M-2167. 48th ICAAC; Washington, DC: 2008.